OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

OTTAWA HULL K1A 0C9

(11) (C) 1,336,687

(21) 609,161

(22) 1989/08/23

(45) 1995/08/15

(52) 167-220

BREVETS
MARQUES DE COMMERCE
DROITS D'AUTEUR
DESSINS INDUSTRIELS
TOPOGRAPHIES DE CIRCUITS INTÉGRÉS
PATENTS
TRADE-MARKS
COPYRIGHT
INDUSTRIAL DESIGN
INTEGRATED CIRCUIT TOPOGRAPHY

(51) Intl.Cl.[5] A61K 31/52; A61K 9/32

(19)(CA) **CANADIAN PATENT** (12)

(54) Process for Preparing Tablets Containing Ibuprofen, APAP and Caffeine, the Products of This Process and the Use of Such Products

(72) Tencza, Thomas M. , U.S.A.
Kim, Chung Bin , U.S.A.

(73) Bristol-Myers Squibb Company , U.S.A.

(57) 9 Claims

1336687

609/61

ABSTRACT OF DISCLOSURE

A process for preparing tablets containing ibuprofen, acetaminophen (APAP) and caffeine which involves preparing separate wet granulations of these ingredients, combining them in a mixture and tabletting this mixture; the products of this process and their use in alleviating pain, and/or reducing fever, and/or reducing an inflammatory process in subjects also being disclosed.

INTRODUCTION

This invention relates to analgesic tablets, and particularly to analgesic tablets that contain a combination of ibuprofen, acetaminophen (APAP) and caffeine.

BACKGROUND OF INVENTION

The use of the combination of acetylsalicylic acid, APAP and caffeine in analgesic tablets has been known for a long time. One such product is marketed by the Bristol-Myers Company under the trademark EXCEDRIN (See "Handbook of Non-Prescription Drugs" 1969 Edition P.34 published by The American Pharmaceutical Association).

More recently, ibuprofen has been approved to some extent by the Food and Drug Administration for over-the-counter sale and has been marketed widely as such. It was thought that a useful combination analgesic product could be made available if ibuprofen was combined with APAP and caffeine in a tablet dosage form.

While investigating the pharmacological availability of the three-active-component analgesic tablet containing ibuprofen, APAP and caffeine as measured by the dissolution rates of these active

ingredients, it soon became obvious that the problem of formulating such a dosage form was much more complicated than was originally anticipated. It was found, for example, that if the three component analgesic tablet product containing ibuprofen, APAP and caffeine was prepared by the direct compression of these actives that the dissolution rates for the active ingredients in these tables left something to be desired.

Another phenomenon was discovered which appeared to portend still more difficulty in preparing analgesic tablets containing ibuprofen, APAP and caffeine as actives that had suitable dissolution rates for the three active ingredients. The dissolution rates of APAP, acetylsalicylic acid and caffeine in tablets containing these three actives, prepared by direct compression and stored under stressed conditions were compared with tablets containing two active ingredients, (i.e. APAP/caffeine and acetylsalicylic acid/caffeine, respectively) also prepared by direct compression and stored under stressed conditions. It was found that for each of the actives, i.e. APAP, caffeine and acetylsalicylic acid the time it took for 80% of each active to dissolve from the direct compression, three-actives tablet was dramatically increased when compared with that found for

the case of the two-actives tablets. In the case for caffeine and APAP, this amounted to about a sixfold increase. In the case of acetylsalicylic acid, it took about 22 minutes for 80% of the acetylsalicylic acid to dissolve in the two actives tablet. But for the three-actives tablet even after 60 minutes, the level of dissolution for acetylsalicylic acid had not reached 80%. These data suggested that when the three active ingredients are pressed into a tablet some sort of interaction takes place among the three ingredients which is some fashion deleteriously effects the dissolution rate of the active ingredients. This raised serious doubts as to whether a suitable analgesic tablet having satisfactory dissolution rates for the active ingredients could be prepared with ibuprofen, APAP and caffeine as active ingredients.

THE INVENTION

It has now been unexpectedly found that the dissolution rates of the active ingredients in an analgesic tablet containing ibuprofen, APAP and caffeine as active ingredients can be maintained at a satisfactory level if each of these ingredients is formed into a separate granulation before mixing them together for

compression into a tablet. These active ingredients are each separately granulated using a wet granulation process and the granulations so prepared are then mixed together, usually with other tablet adjuvants, and then tabletted in conventional punchpress type machines.

Thus the present invention provides a process for preparing a tablet containing ibuprofen, acetaminophen and caffeine as pharmaceutically active ingredients comprising:
claim 1

(a) preparing separate wet granulations of each of ibuprofen, acetaminophen and caffeine suitable for tabletting;

(b) forming a mixture suitable for tabletting containing said ibuprofen granulation, said acetaminophen granulation and said caffeine granulation prepared in step (a) and

(c) tabletting the mixture prepared by step (b)

The invention also provides in certain aspects tablets prepared in accordance with such process and the use of such tablets for alleviating pain and/or reducing fever and/or reducing an inflammatory process in a subject.

In the attached drawings:

Fig. 1 is a graph showing the initial dissolution rates and the dissolution rates after storage for 1 month at 40°C and 75% relative humidity (designated by the expression H/H) for the active ingredients, i.e. ibuprofen (IBU), acetaminophen (APAP) and caffeine contained in tablets prepared by first preparing separate wet granulations of the actives and then mixing and compressing them into tablets in accordance with the present invention (Formula CW 4708-29B);

Fig. 2 is a graph similar to that shown in Fig. 1 except that the tablets tested were prepared by direct compression of IBU, APAP and caffeine, that is to say that the IBU, APAP and caffeine were used in the form of powders or granules as distinguished from a granulation form (Formula CW 3708-28B).

In the pharmaceutical tabletting art, a distinction is made between a granulation form and a granular form of an ingredient that is to be compressed into a tablet. The granulation form of an ingredient (e.g. ibuprofen) is prepared by a wet granulation process that begins with the ingredient in powder or granular size. Either or a combination of the latter two are wetted with a granulation solution, usually containing a binder to form a crumbly mass which is then ground and sized. Such a product is referred to as a granulation product and in the case of ibuprofen it can be referred to as an ibuprofen granulation. By contrast, granular ibuprofen, although not available commercially, could theoretically be used to refer to ibuprofen which has not been processed in this fashion. In this case, the term granular is an expression of the particle size of the ibuprofen rather than the manner in which the ibuprofen was processed and is often used to distinguish the material from its finely divided or powder form. By an extension of this nomenclature, we can and do refer to APAP granulation and caffeine granulation on the one hand and to granular APAP and granular caffeine on the other hand.

A further way of distinguishing between the granulation form and the granular form of material is by way of the bulk density and the particle size of the substance. The particles of the

granulation form of a drug generally have a lower bulk density and larger particle size (e.g. No. 8 mesh to No. 20 mesh) whereas the particles of the granular form of a drug have a higher bulk density than the granulation form of the drug and a smaller particle size (e.g. No. 8 mesh to No. 80 mesh).

Still a further way of distinguishing between the granulation form and the granular form of a material takes advantage of the fact that in preparing the former a granulating solution is employed which usually contains a binder (e.g. starch) that becomes incorporated in the granulation. The binder generally comprises from about 0.5% to about 6% by weight of the granulation based on the total weight of the granulation with the preferred range being from about 1% to about 4 or 5% on the same weight basis.

The quantity of ibuprofen that will be contained in the tablets of this invention might vary depending, among other things, on the number of tablets that are to be used to deliver an effective analgesic dose. Generally, however, each tablet will contain from about 50 mg. to about 400 mg. of ibuprofen. In the preferred case, the effective analgesic dose will be delivered with two tablets each of which will contain about 50 mg. to about 400 mg. of ibuprofen.

Similar consid rations obtain with respect to quantity of APAP and caffeine contained in each tablet of this invention. Thus, generally each tablet will contain from about 150 mg. to about 500 mg. of APAP and from about 30 mg. to about 130 mg. of caffeine. In the preferred cases, two tablets are used to delivery an effective dose, each tablet will contain from about 150 mg. to about 500 mg. of APAP and from about 30 mg. to about 130 mg. of caffeine.

In addition to the above mentioned ingredients, the tablets of this invention may also contain adjuvants that are commonly added in tablet manufacturing to form more elegant tablets or to facilitate the tabletting process. These may include such agents as fillers, disintegrants, lubricants, binders, etc. By way of illustrating particular adjuvants that may be employed in preparing the present tablets, mention may be made of the following:

fillers; lactose, microcrystalline cellulose, etc.

disintergrants; starch, Ac-Di-Sol*, CROSPOVIDONE* XL-10, etc.

lubricants, stearic acid, Mg-Stearate, etc.

flow agents; Cab-O-Sil* (Silicone Dioxide), etc.

* Trademark

As indicated above, it is a feature of the present invention that each of the active ingredients be prepared as a granulation before it is mixed with the other ingredients to be pressed into a tablet. A variety of wet granulation procedures, known to those skilled in the tabletting art, may be used in preparing the individual granulations that are useful for the purposes of the present invention. Generally, the wet granulation process will involve moisturizing the powdered active ingredient with a solution of a bonding agent to cause a certain amount of agglomeration to bring the powder to the consistency of a crumbly mass. This mass will then be sized and dried and the resulting dried mass will be broken up to give granulation particles of the desired size.

A preferred wet granulation procedure useful for preparing the granulations of active ingredients useful for the purposes of the present invention may be described in the following terms. The first step in the wet granulation process consists of uniformly mixing the powdered active agents with the diluent. The mixture is passed through a No. 10 to No. 30 mesh screen and subjected to additional blending. This is followed by careful moistening with the proper binding solution until the mixture has the consistency

of a crumbly mass. The wet mass is then screened through a No. 6 mesh to a No. 20 mesh screen using an oscillator. The wet particles are then dried in an Fluid Bed Dryer at about 50°C. After drying, the particles are broken up and passed through the proper screen to obtain the desired particles size.

The tablets of the present invention may be used in the treatment of those conditions for which over-the-counter analgesics are generally recommended. These include the treatment of pain from neural and muscular sources, fevers, inflammation of the kind that responds salicylate therapy.

It has also been found advantageous in this invention to sometimes apply a film coating to the tablets. This provides tablets that have satisfactory chemical and physical stability characteristics. A variety of film forming polymers are known in this art that are useful for this purpose. These include such polymers as polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, polyethylene glycols and mixtures thereof. These film forming polymers will generally be applied from a liquid composition

containing them. Such liquid compositions, aside from the film forming polymer or polymers may also contain surface active agents, plasticizers, film smoothing agents, coloring agents and antifoaming agents. The vehicle for the liquid coating composition will generally be an aqueous vehicle in which the film forming polymers are suspended. The older solvent systems can also be used as the vehicle.

The film coating may be applied to the tablets of this invention in any suitable manner known to those skilled in this art. One highly satisfactory procedure may be described as follows:

1. Place the tablet cores into a 24" Accela Cota pan (perforated pan) and turn on the exhaust and heater. Pre-heat the tablets to 42°C while jogging the pan.

2. The film coating solution is sprayed through spray guns using the following parameters.

   pan speed: 10-16 rpm
   spray rate: 30ml-40ml/min.
   No. of spray guns: 2
   Inlet temperature: 40-42°C
   Outlet temperature: 38-40°C
   Atomization air pressure: 20 psi
   Amount of film (as solid): 2%-3% (w/w) of tablets

3. At the c mpletion of the coating, the film coated tablets are dried while jogging the coating pan until outlet temperature reaches 42°C.

The following examples are given to further illustrate this invention. It is to be understood, however, that this invention is not limited thereto.

The trade designations for materials listed below appear in this specification and are identified chemically by the definition following each trade designation:

DC APAP 90 = 90% acetaminophen granulation,

Crospovidone XL-10 = cross linked, insoluble homopolymers of N-vinyl-2-pyrrolidone,

Povidone (K29-32) = Polyvinylpyrrolidone,

Hydroxypropylmethyl cellulose = glycol ether of hydroxymethyl cellulose,

Arlacel* 20 = sorbitan laurate,

Tween* 20 = polysorbate 20,

Color White = Titanium dioxide in aqueous propyleneglycol base,

Antifoam = Simethicone NF (polymethylsiloxane)

In the Examples given below, the ibuprofen, ASA, APAP and caffeine are employed as particles made by a wet granulation process. The details for the preparation of each granulation active ingredient or the physical data that characterize these granulations are as follows:

A. Preparation of Ibuprofen Granulation

1. Mix a formula amount of ibuprofen and a formula amount of corn starch in a Ribon type blender.

2. Dissolve a formula amount Povidone in hot water (granulating solution; 3.2%)

3. Granulate the mixture of ibuprofen and corn starch with the Povidone solution, and add a formula amount of microcrystalline cellulose and Crospovidone XL-10, and mix well.

4. Pass wet granulation through a Tornado mill with 1/2" plate and dry it in a Fluid Bed Dryer.

5. Oscillate dry granulation through a No. 10 mesh screen.

B. Preparation of DC APAP 90 Granulation

Ingredients:

Acetaminophen fine powder
Corn starch
Croscarmellose Sodium
Povidone
Stearic Acid

Process:

Refer to U.K. Patent GB 2090739A (Applicants; Monsanto, Inventors; Stephen H. Vogel)

Particle size:

On 30 mesh : 10.0% maximum
On 30 + 40 mesh : 30.0% maximum
On 30 + 40 + 80 mesh : 60.0% minimum

C. Preparation of Caffeine Granulation

1. Mix a formula amount of caffeine and 1/7 of a formula amount of corn starch in a Hobart mixer.

2. Add hot water and the remaining amount of corn starch, and granulate.

3. Pass wet granulation through a Tornado mill with 1/2" plate.

4. Dry wet granulation in a Fluid Bed Dryer.

5. Oscillate dry granulation through a No. 14 mesh screen.

D. Acetylsalicylic Acid Starch Granulation (12/50)

Process: Dry Compaction Method.
Particle size:
On 12 mesh : 0.4% maximum
On 14 mesh : 3.0% to 15.0%
On 40 mesh : 75.0% minimum
On Pan : 10.0% maximum

E. APAP Starch Granulation 145

Ingredients:
Acetaminophen fine powder
Corn starch
Erythrobic Acid
Polysorbate 80
Povidone

Process:
Refer to U.K. Patent GB 2090739A (Applicants; Monsanto, Inventors; Stephen H. Vogel)

Particle size:
On 30 mesh : 10.0% maximum
On 30 + 40 mesh : 30.0% maximum
On 30 + 40 + 80 mesh : 60.0% minimum

Example 1

Formula CW-3589-71

I Core Tablets:

Ingredients	mg/tablet
DC APAP 90 (granulation)	361.0 (equiv. to 325 mg of APAP)
Ibuprofen (granulation)	100.0
Caffeine (granulation)	50.0
Corn Starch	52.0
Microcrystalline Cellulose	21.0
Crospovidone XL-10	1.0
Povidone (K29-32)	3.0
Stearic Acid	3.0
	591.0

IT Film Coating:

Ingredients	mg/tablet
Povidone (K29-32)	0.95
Hydroxypropylmethyl Cellulose	5.05
Propylene Glycol	1.13
Arlacel 20	0.71
Tween 20	0.47
Mineral Oil Light	0.19
Color White	3.31
Antifoam	0.01
	11.82

Preparation of the Core Tablets

1. Mix DC APAP 90, Ibuprofen granulation (ibuprofen, corn starch, microcrystalline cellulose, Crospovidone XL-10 and Povidone (K29-32)) and caffeine granulation (caffeine and starch) in a Twin Shell Blender for 15 minutes.

2. Screen stearic acid through a No. 30 mesh screen and mix it with the above mixture in a Twin Shell Blender for 5 minutes.

3. Compress Tablets on a rotary press using 7/16" standard concave punches.

Coating Procedure

A coating composition is prepared having the following formula:

	% (w/w)
Water	84.00
Povidone (K29-32)	1.00
Hydroxypropylmethyl Cellulose	5.34
Propylene Glycol	1.20
Arlacel 20	0.75
Tween 20	0.50
Mineral Oil Light	0.20
Color White T-510W	7.00
Antifoam	0.01
	100.00

This coating was applied to the core tablets described above using the following procedure:

1. Place the 6 KG compressed tablets into 24" Accela Cota pan and turn on the exhaust and heater. Pre-heat the tablets to 42°C while jogging the pan.

2. 0.132 Kg of the film coating solution is sprayed through spray gums using the following parameters;

Pan Speed: 14 rmp,	Spray rate: 30 ml/min.
No. of Spray Gums: 2	Inlet Temperature: 40°C
Outlet Temperature: 38°C	Atomization Air Pressure: 20 psi.

3. At the completion of the coating, the film coated tablets are dried while jogging the coating pan until outlet temperature reaches 42°C..

Example 2

Formula CW 3708-29B

Formula	mg/tablet
Ibuprofen (granulation)	150.0 (100 as ibuprofen)
DC APAP 90 (granulation)	277.8 (250 as APAP)
Caffeine (granulation)	100.0 (65 as caffeine)
Stearic Acid	3.0
	530.8

Procedure for tablet preparation:

1. Mix DC APAP 90 granulation, ibuprofen granulation (ibuprofen, corn starch, microcrystalline cellulose, Crosspovidone XL-10 and Povidone (K29-32)) and caffeine granulation (caffeine and starch) in a Twin Shell Blender for 15 minutes.

2. Screen stearic acid through a No. 30 mesh screen and mix it with the above mixture in a Twin Shell Blender for 5 minutes.

3. Compress tablets on a rotary press using 7/16" standard concave punches.

For the purposes of comparison, tablets of the following formulations were prepared:

Formula CY 3513-1

Formula	mg/tablet
Caffeine starch granulation	100.0 (65 as caffeine)
Acetylsalicylic acid starch granulation (12/50)	277.8 (250 as acetylsalicylic acid)
APAP starch granulation 145	277.8 (250 as APAP)
Stearic Acid	3.0
	658.6

Process for preparing tablets:

1. Mix caffeine starch granulation, acetylsalicylic acid starch granulation and APAP starch granulation in a Twin Shell Blender for 15 minutes.

2. Screen stearic acid through a No. 30 mesh screen and mix it with the above mixture in a Twin Shell Blender for 5 minutes.

3. Compress tablets on a press using 7/16" standard concave punches.

Formula CW 3708-30

Formula	mg/tablet
Acetylsalicylic Acid	250.0
APAP	250.0
Caffeine	65.0
Microcrystalline cellulose	100.0
Stearic Acid	3.0
	667.5

Process for preparing tablets:

1. Mix acetylsalicylic acid, caffeine and microcrystalline cellulose in a Twin Shell blender for 15 minutes.

2. Screen stearic acid through a No. 30 mesh screen and mix it with the above mixture in a Twin Shell Blender for 5 minutes.

3. Compress tablets on a press using 7/16" standard concave punches.

The active ingredients were used in the Formula CW 3708-30 in the following forms:

Acetylsalicylic acid - crystals from 20 mesh to 100 mesh
Caffeine - powder or granular: 20 mesh to 100 mesh
APAP - powder or granular: 12 mesh to 100 mesh

Under actual use conditions tablets are likely to be exposed to stress conditions, such as high humidity, which can have an effect on the dissolution rate of the actives in a tablet. With this in mind, the tablets tested were first subjected to stress which took one of two forms. One form entailed storing the tablets in a petri dish for 4 weeks at high humidity. The other form was to store the tablets in a slide box at high humidity for 4 weeks. Slide boxes are not well sealed from the atmosphere and consequently their contents can be effected by a high humidity environment.

To compare the release rates of active ingredients of tablets mbodied in the present invention (Formula CW 3708-29B,) with comparable tablets containing acetylsalicylic acid rather than ibuprofen (CY 3513-1, and CW 3708-30,) the following tests were carried out:

(a) the acetylsalicylic acid containing tablets Formula CY 3513-1, were stressed by storing the tablets in a slide box at high humidity for 4 weeks before measuring the release rates of the active ingredients;

(b) the acetylsalicylic acid containing tablets Formula CW 3708-30 and the ibuprofen containing tablets of this invention, Formula CW 3707-29B, were both stressed by storing these tablets at high humidity in a petri dish for 4 weeks before measuring the release rate of the active ingredients;

(c) The protocol for testing the dissolution rates for the active ingredients in each species of tablet was the same and was as follows:

Dissolution Rate Test:

The dissolution method used to evaluate these tablets employs

the dissolution test described in the USPXXI p. 14. The dissolution test calls for the use of 900 ml. water maintained at 37°C and the USP paddle, known as Apparatus 2, rotated at 50 rpm.

The tablet is placed in the beaker of water or buffer solution (pH 7.2) and after 45 minutes of paddle rotation at 50 rpm, an aliquot of solution is analyzed for acetylsalicylic acid, acetaminophen, caffeine and ibuprofen content.

The analysis can be done via high pressure chromatography or via spectrophometric analysis using a multi-component analysis on HP&450 or HP8451 spectrophotometer.

As a criteria for acceptability, applicants have adapted a dissolution rate such that at least 75% of the tablet dissolves in under 45 minutes.

The results of these tests are summarized in Table I below. The release of acetylsalicylic acid was measured as acetylsalicylic acid (ASA).

The entries in this Table under the heading T_{25}, T_{50}, T_{75}, T_{80}, T_{85} represents the time in minutes it took for 25%, 50%, 75%, 80% or 85%, respectively of the active ingredient in question contained in the tablet to be released.

An appr ciation for the merits of the tablets of this invention can be seen by comparing the dissolution values under the heading "T_{75}" for each of the active ingredients. Thus, with the tablets of the present invention (CW3707-29B) it took 7.7±.6 minutes for 75% of the ibuprofen to be released from these tablets. This is to be compared with the ASA release rates for formulas CW3708-30 and CY 3513-1. For tablets CW-3708-30, and tablets CY 3513-1, the values were more than 60 minutes, and from 24 to more than 48 minutes, respectively to reach a level of a 75% release of ASA from the respective tablets. Similar results hold for the other active ingredients, that is APAP and caffeine, as the data also demonstrate.

To demonstrate the effect of the wet granulation of actives (i.e. ibuprofen, APAP and caffeine) on the dissolution rates of these materials when they are compressed into tablets and to compare these dissolution rates for the same materials in tablets prepared by the direct compression of these actives in particle forms other than granulations as understood herein an additional formulation (identified as CW 3708-28B) of tablets prepared from direct compression of said non-granulation actives was made. The formula for these tablets and its process for preparation is given below:

TABLE I

FORMULA	Active	T_{25}	T_{50}	T_{75}	T_{80}	T_{85}	% Diss 60 Min.**	Totals**
CW-3708-29B	IBU	1.8±.1	3.6±.1	7.7±.6	9.7±1.7	1.3±2.9	89,98,95,94	89,97,97,94
	APAP	.1±.2	2.1±.3	3.3±.5	3.6±.4	4.1±.4	106,104,102,104	106,104,102,104
	CAFF	.8±.3	3.0±.5	4.5±.7	5.1±.8	5.7±.9	103,94,107,99	103,94,107,99
CW 3708-30								
	ASA	19±2	45±6	>60	>60	>60	57,58,67,58	84,69,88,88
	APAP	12±1	27±3	53±6	53- >60	>60	75,79,83,77	102,104,102,103
	CAFF	6±<1	12±1	27±2	32±3	39±6	97,93,89,95	100,93,91,95
CY3513-1	ASA	9	18	*				
	APAP	4	8	16				
	CAFF	5	9	14				

* 4 tablets tested which had a reading from a high of 48 or more to a low of 24.
** Values given for tests on 4 separate tablets.

Formula CW 3700-28B
Direct Compression 3 Actives
(IBU/APAP/Caff.)

Formula	mg/tablet
Ibuprofen	100.0
APAP	250.0
Caffeine	65.0
Microcrystalline cellulose	100.0
Stearic acid	2.5
	517.5

Process for preparing tablets:

1. Mix ibuprofen, APAP, Caffeine and microcrystalline cellulose in a Twin Shell Blender for 15 minutes.

2. Screen streaic acid through a No. 30 mesh screen and mix it with the above mixture in a Twin Shell Blender for 5 minutes.

3. Compress tablets on a press using 7/16" standard concave punches.

The form of the ibuprofen, APAP and caffeine used in this formulation is as follows:

Ibuprofen - fine powder from 25 microns to 60 microns
APAP - powder or granular
particle size : 12 mesh to 100 mesh
Caffeine - powder or granular
particle size : 20 mesh to 100 mesh

The dissolution rate of tablets of this formula CW 3708-28B and those of this invention [CW-3708-29B, see Example 2] was measured for each of the active ingredients (i.e. IBU, APAP and caffeine) using the protocol of the "Dissolution Rate Test" also described above. The results of test are summarized in the attached drawings.

Fig. 1 summarizes that dissolution rate data for ibuprofen/APAP/caffeine tablets prepared in accordance with the present invention (Formula CW 3709-29B) from three separate wet granulations of ibuprofen (IBU), APA and caffeine. These dissolution rates were measured for each of the actives from tablets which were unstressed and those which were stressed, (i.e. stored for one month at 40°C and 75% relative humidity). The dissolution rate for a particular active from an unstressed tablet is designated in the graph by the legend "Initial". Thus, for example, the curve identified by the legend "APAP, Initial" summarizes the dissolution rate data for APAP obtain from unstressed tablets containing ibuprofen, APAP and caffeine. In an analogous manner, the dissolution rate for a particular active ingredient from a stressed tablet (i.e. a tablet stored for one month of 40°C and 75% relative humidity) is designated by the legend "H/H", Similarly, for

example, the curve identified by the legend "APAP at H/H" summarizes the dissolution rate data for APAP obtained from stressed tablets containing ibuprofen, APAP and caffeine. These designations are carried over to the data for the other active ingredients as well as into the data summarized in the graph of Fig. 2.

A study of Fig. 1 will reveal that for the tablets of this invention in their unstressed condition, 80% of each of the active ingredients dissolved in under 5 minutes. The same was true for the tablets in the stressed condition except for ibuprofen for which it took about 10 minutes for 80% of the ibuprofen to dissolve.

These data are to be compared with the similar data obtained from tablets of IBU/APAP/caffeine prepared by direct compression as understood herein. The data of the latter are summarized in Fig. 2. With the unstressed tablets of this type, none of the active ingredients dissolved to a level of 80% in less than 5 minutes as was the case with the tablets of this invention. (See curves captioned "Caffeine, Initial", "APAP, Initial" and "Ibuprofen, Initial"). As a matter of fact it took more than 10 minutes for the APAP and about 25 minutes for ibuprofen to reach this level of dissolution.

The difference in dissolution rate for the actives between that obtained from the tablets of the present invention and that obtained from direct compression tablets, as understood herein, is even more dramatic when the tablets compared are those that have been stressed (i.e. stored for 1 month at 40°C and 75% relative humidity). Thus it took just under about 5 minutes for 80% of the caffeine to dissolve from the stressed tablets of this invention. (See curve "Caffeine at H/H" in Fig. 1.) This is to be compared with the curve "Caffeine at H/H" in Fig. 2 for the direct compression tablets from which it took as much as about 35 minutes for 80% of the caffeine to dissolve from these stress tablets.

These differences are still more remarkable for APAP and ibuprofen. For the stressed tablets of the present invention it took about 4 minutes for 80% of the APAP to dissolve (See curve "APAP at H/H, FIg. 1). This is to be compared with curve "APAP at H/H" in Fig. 2 which indicates that it took 60 minutes or more for 80% of the APAP to dissolve from the stressed direct compression tablets. Even more dramatic differences in dissolution rate between the respective tablets is to be seen with respect to ibuprofen. In the stressed tablets of this invention, it took about 10 minutes for 80% of the ibuprofen to dissolve (See Curve "Ibuprofen at H/H in Fig. 1). In the case of the stressed direct compression tablet, even after 60 minutes the level of ibuprofen dissolution had only reached about 50% (See curve "Ibuprofen at H/H" in Fig. 2).

Another unexpected feature of the tablets of the present invention is the surprisingly good stability characteristics that they exhibited. No evidence of physical incompatibilities was noted such as eutectic formations. Chemical stability is satisfactory in high density polyethylene and polystyrene bottles with safety and non-safety caps at high humidity and 125°F after three months of storage.

Physical stability of the tablets of this invention is satisfactory with regard to appearance and disintegration time in all packages at all conditions except 125°F after three months storage. A temperature of 125°F is an extreme condition for ibuprofen containing tablets.

Table II summarizes the data collected in the stability testing. The tablets used in these stability tests were those of formula CW-3589-71 (See Example 1 above). The characteristics tested were disintegration time measured in minutes (see upper half of Table II) and appearance (See lower half of Table II). The shorthand terms appeared in the headings of the columns in Table II have the following meaning:

HD/PE = high density polyethylene;

P/S = polystyrene.

TABLE II

Physical Stability of Tablets CW-3589-71 with Ibuprofen

Tests	Packages	HD/PE Bottle Safety cap	HD/PE Bottle Non-safety cap	HD/PE Bottle Screw-cap	P/S Bottle Safety cap	P/S Bottle Non-safety c
Disintegration (in min.)						
1 Month	RT	2	2	2	2	2
	104°F	2	2	2	2	2
	H/H	2	2	2	2	2
	125°F	3-11	3- >10	3-8	3-7	3-7
2 Month	RT	2	2	2	2	2
	104°F	2-3	2-3	2-3	2-3	2-3
	H/H	2-3	2-3	2-3	2	2
	125°F	4-7	9- >20	4-14	4-11	4-8
3 Month	RT	2	2	2	2	2
	104°F	2-3	2-3	3	2-3	2-3
	H/H	2-3	2-3	3-7	2-3	2-3
	125°F	4-7	5- >10	5-7	4- >10	7-8
Appearance						
1 Month	RT	OK	OK	OK	OK	OK
	104°F	OK	OK	OK	OK	OK
	H/H	OK	*	*	*	*
	125°F	****	****	****	****	****
2 Month	RT	OK	OK	OK	OK	OK
	104°F	OK	OK	OK	OK	OK
	H/H	**	**	**	**	**
	125°F	****	****	****	****	****
3 Month	RT	OK	OK	OK	OK	OK
	104°F	**	**	**	**	**
	H/H	***	***	***	***	***
	125°F	****	****	****	****	****

Note: * - very very slight color change; ** - very slight color change
*** - slight color change; **** - change in color

What is claimed is:

1. A process for preparing a tablet containing ibuprofen, acetaminophen and caffeine as pharmaceutically active ingredients comprising:

(a) preparing separate wet granulations of each of ibuprofen, acetaminophen and caffeine suitable for tabletting;

(b) forming a mixture suitable for tabletting containing said ibuprofen granulation, said acetaminophen granulation and said caffeine granulation prepared in step (a) and

(c) tabletting the mixture prepared by step (b)

2. A process according to Claim 1 including the further step of film coating the tablet resulting from step (c) of Claim 1.

3. A process according to Claim 1 wherein the active ingredients are employed in amounts such that each tablet contains:

(a) from about 50 mg to about 400 mg of ibuprofen;

(b) from about 150 mg to 500 mg of acetaminophen, and

(c) from about 30 mg to about 130 mg of caffeine.

4. A process according to Claim 3 including the further step of film coating the tablet prepared by Claim 3 with a composition containing a film forming polymer selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, sodium carboxymethyl cellulose, polyethylene glycols and mixtures thereof.

5. A tablet prepared in accordance with the process of Claim 1.

6. A tablet prepared in accordance with the process of Claim 2.

7. A tablet prepared in accordance with the process of Claim 3.

8. A tablet prepared in accordance with the process of Claim 4.

9. The use of a tablet of any one of claims 5, 6, 7 or 8 for alleviating pain, and/or reducing fever, and/or reducing an inflammatory process in a subject.

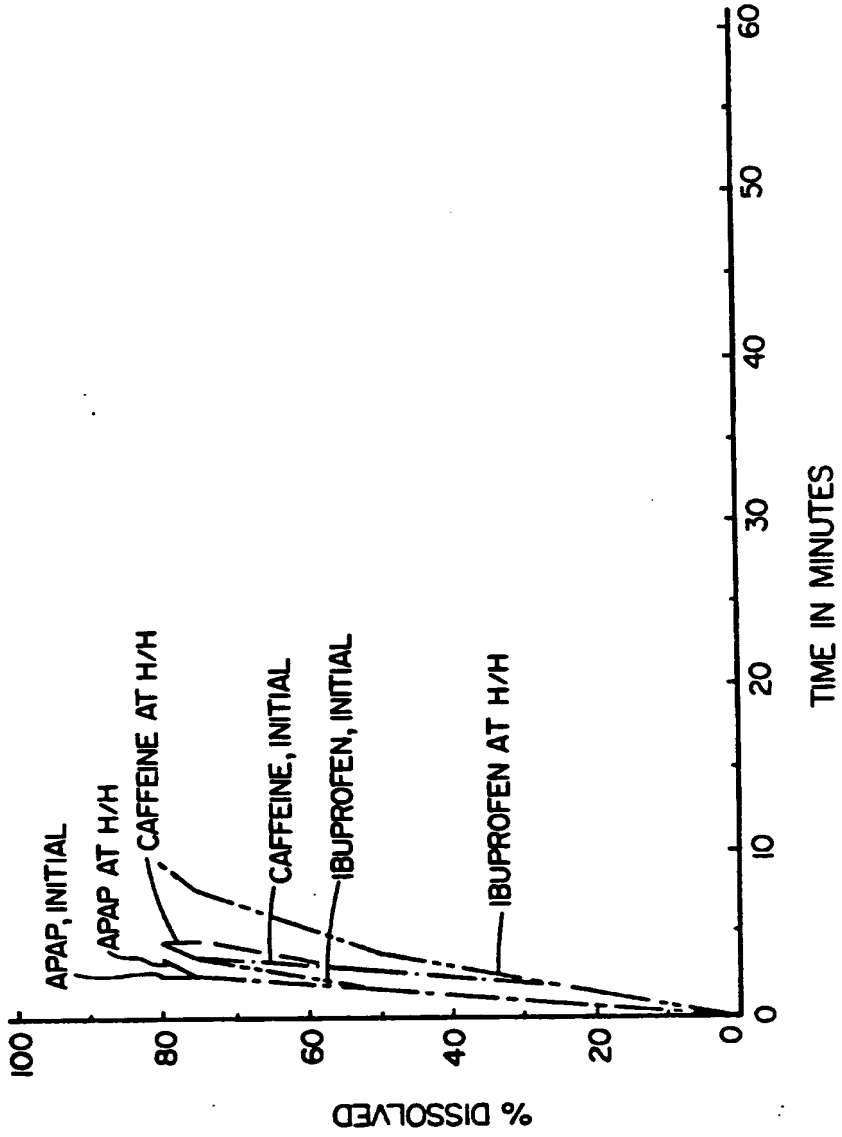
APAP, INITIAL
APAP AT H/H
CAFFEINE AT H/H
CAFFEINE, INITIAL
IBUPROFEN, INITIAL
IBUPROFEN AT H/H
% DISSOLVED
100
80
60
40
20
0
0
10
20
30
40
50
60
TIME IN MINUTES

FIG. 1

1336687

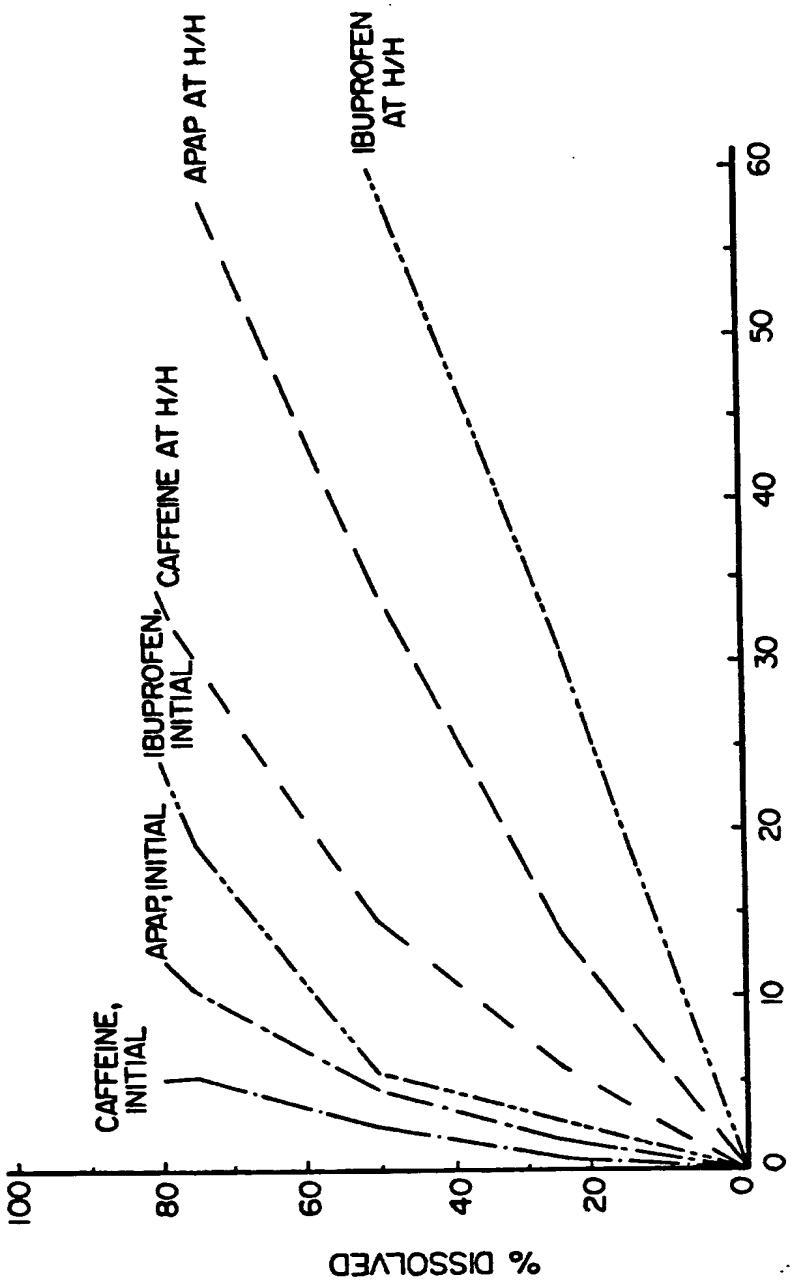

FIG. 2